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Applicant(s): Jeffrey W. RUBERTI *et al.*

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Title: SYSTEMS AND METHODS FOR CONTROLLING AND FORMING  
POLYMER GELS

United States Patent and Trademark Office  
Randolph Building  
401 Dulany Street  
Alexandria, VA 22314

**DECLARATION OF STEPHEN SPIEGELBERG**

I, Stephen Spiegelberg, do hereby declare as follows:

1. I received my Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology (MIT) in 1993. I have been engaged in the study of polymers, such as vinyl polymers for *in vivo* use over 15 years. I have authored or co-authored at least 50 peer-reviewed papers and presentations, several book chapters and co-invented several US Patents related to polymeric materials and their use in medical prosthetics. I am a co-founder and currently the President of the Cambridge Polymer Group, Inc.

2. I understand that claim 113 in the captioned patent application has been rejected allegedly as being anticipated by or, in the alternative, as being unpatentable over Hyon (US 4,663,358), or Tanihara (US 5,880,216). I also understand that claim 113-119 have been rejected allegedly as being anticipated by or, in the alternative, as being unpatentable over Tanihara (US 5,880,216), Ku (US 5,981,826), Yao (US 6,268,405), or Okamura (JP 04338326).

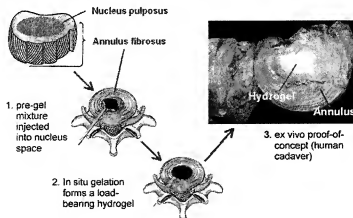
In the Office Action issued October 18, 2007, regarding the injectability of the prior art hydrogels, the examiner contends that the experiment as described in the declaration was not commensurate in scope with what is actually being claimed.

In order to address the issue and to demonstrate that the none of the processes disclosed in the cited references would yield "injectable hydrogel", I submit the following:

3. Claimed invention is not taught in the cited references because the claimed injectable physically cross-linked hydrogel is formed without chemical cross-linkers, irradiation or thermal cycling. The injectable solution of the invention forms a hydrogel in the body cavity without being subjected to ionizing radiation, reducing temperature below 0°C, or have additional chemical reactants added to it in order for the liquid material introduced into the cavity to form a hydrogel. The claimed product is clearly superior to what is currently available commercially, the system provided unexpectedly improved properties of the claimed injectable hydrogels and solved a long felt but unmet needs of injectable system.

Advantages of the invention include (as disclosed in the application, see paragraphs [0010—0014], [0026], [0031], [0044], and [0101] of the published application, for example):

- Allows for a minimally invasive surgical procedure;
- Porous, highly hydrated system allows fluid and nutrient flow from endplates;
- Provides space-filling for optimal load-transfer to the annulus fibrosis;
- No chemical reaction, so no by-products or exotherm; and
- Biocompatible components.



**Figure 1.** Source: <http://www.hydrospace.com/technology.html>

Figure 1 demonstrates that pre-gel mixture (see step 1 in Figure 1, an injectable solution) is injected into a nucleus space (see step 1 in Figure 1, a body cavity), which undergoes in situ gelation and forms a load bearing hydrogel (see step 2 in Figure 1,

without any further steps as required for hydrogels known in the art). Further *ex vivo* proof of the system is shown in human cadaver (see step 3 in Figure 1).

Please note as the claims recite, "injectable solution for injection into a body cavity" and "the solution of the polymer hydrogel gels *in situ* after the injection" clearly distinguish the claims from the cited references or any combination of the cited references. Because, none of the cited references or any combination thereof provide "an injectable solution for injection into a body cavity", wherein the "hydrogel is formed without chemical cross-linkers, irradiation or thermal cycling", and the "hydrogel gels *in situ* after the injection", which is further supported by additional experiments submitted herewith (see for example, Figure 2, Tests 1-4).

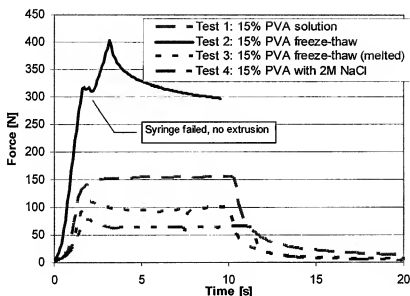


Figure 2.

4. Regarding the injectability experiments, further to my declaration of March 2, 2007, we have conducted four additional experiments to demonstrate that while the claimed materials are injectable and spontaneously form gel after injection, the materials disclosed in the references are not.

#### **Methods for testing injectability:**

In the following tests, we present data that support the claims that polymer hydrogel gels *in situ* after the injection without a further processing step. This sequence of *in situ* hydrogel formation after the injection is not possible using the gels disclosed in the cited references. Three syringes were tested for injectability. The solutions tested all contained 15% w/w PVA (see Table 1). This concentration is

consistent with claim 115 as presented and is also consistent with Tanihara *et al.* (see abstract), Ku *et al.* (see column 4, line 34), Yao *et al.* (see column 3, line 62) and Hyon *et al.* (see claim 4).

**Table 1.**

Test	PVA %	Water %	Other ingredient	Other	Comments
Test 1	15%	85%	None	-	Ungelled, injectable, never forms hydrogel after injection
Test 2	15%	85%	None (freeze-thaw)	-	White opaque gel after 24 hours. Not injectable at room temperature.
Test 3	15%	85%	None (freeze-thaw)	-	White opaque gel after 24 hours. Injectable after melting (transparent). Never forms hydrogel after injection.
Test 4	15%	85%	NaCl	2M	Transparent injectable solution forms hydrogel after injection

*Test 1* is a control containing only a PVA solution with no further processing (see Table 1, Figure 2, Test 1).

*Test 2* is the freeze-thaw procedure as described in Tanihara, Ku, Okamura, Yao, and Hyon (see Table 1, Figure 2, Test 2).

*Test 3* is a repeat of test 2, but with the freeze-thaw gel melted to prove that this system does not re-gel (see Table 1, Figure 2, Test 3).

*Test 4* is the procedure described in the current application using 2M NaCl, which is consistent with the claims of the current application (see Table 1, Figure 2, Test 4).

The compositions are listed below with pictures for each test (see Table 1, Tests 1-4). Each solution was made fresh, except for the freeze-thaw material that started with a 15% solution of PVA which was then allowed to gel overnight using the process in the cited references. The PVA solution alone (test 1) remained transparent and did not gel. After the freeze-thaw process in test 2, an opaque hydrogel formed. The PVA-NaCl solution was initially transparent after mixing and during injection but subsequently gelled to a cloudy, elastic semi-solid hydrogel. The injectability testing was done in a custom-built injection fixture consisting of a clear acrylic tube topped with a polyethylene standoff for a 5-mL syringe tipped with a 18 G needle. A 100 lb load cell was fitted to the syringe plunger using polyethylene attachments. A linear motion was then applied to the fixture using a linear actuator moving at a rate of 3 mm/s and

the amplitude of the force on the syringe was measured by the load cell. Approximately 4 ml of solution was ejected from each syringe during the test, when possible. Photos of the injection or failure to inject were taken before the test, during linear actuator movement, after the test, and 1-hour after the test to check for gelation after injection (see attached photographs from Tests 1-4).

**Test 1: PVA in deionized water.**

The solution was transparent at all times, and injected easily. The starting syringe appeared visually clear indicating no gelation through crystallization, and the force required to inject the solution was low. The resulting liquid remained liquid and transparent after an hour of monitoring, showing no sign of gelation and instead remained a liquid. After 24 hours of storage in the syringe, the material had still not formed a hydrogel. (See Figure 2 and photographs under Test 1).

**Test 1: 15% PVA in deionized water.**



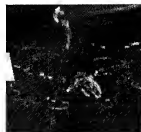
Pre-test



During injection



Immediately after injection



1 hour post injection (no gelation)

Note fluid emerging from  
needle

Note strands of liquid  
sample

**Test 2: PVA in deionized water, 1 freeze-thaw cycle.**

After the initial sample preparation (freeze-thaw) and the 24 hour waiting period, the room temperature syringe was opaque. During the injection test, the injection apparatus could not extrude any of the room temperature sample from the syringe, instead building a force in excess of the rated range of the transducer, eventually fracturing the syringe. (See Figure 2 and photographs under Test 2).

**Test 2: 15% PVA in deionized water – freeze-thaw.**

During injection (no material injected)  
Pre-test



No image available since  
No material ejected

Post-injection

Note cloudy gel

**Test 3: PVA in deionized water, 1 freeze-thaw cycle, melted.**

After the initial sample preparation (freeze-thaw) and the 24 hour waiting period, the room temperature syringe was opaque. After immersion in boiling water, the melted sample was transparent. Upon loading into the injection apparatus, the melted solution extruded easily; however, after 1 hour, the sample did not form a hydrogel and instead remained a liquid. After 24 hours of standing, the material had still not formed a hydrogel. (See Figure 2 and photographs under Test 3).

**Test 3: 15% PVA in deionized water – freeze-thaw and melted.**

Pre-test



During injection



Post-injection



1 hour post-injection (no gelation)

Note strands of liquid sample  
indicating no gelation

**Test 4: PVA in 2M NaCl.**

After the initial sample preparation the syringe was transparent indicating no gelation. Hydrogel was formed by controlling the gelation rate by changing Flory Interaction parameter of the solution until the final desired Flory parameter is reached, which is between 0.25 and 1.0 (as disclosed in the application, see paragraphs [0020], [0030], [0031], and [0057] of the published application, for example). During the injection test, the solution extruded easily, and formed a shape-holding partially-translucent hydrogel after 1 hour indicating subsequent gelation (see Figure 2 and photographs under Test 4).

**Test 4: Fresh 15% PVA in 2M NaCl.**

Pre-test



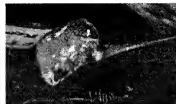
During injection

Note three dimensional  
shape indicating gelation

Note material  
emerging from needle



Post injection



1 hour post injection (gelation)

5. Regarding Tanihara *et al.* disclosure, please note that the disclosure is not relevant to the claimed invention. Tanihara describes a chemically modified repeat unit to improve heat resistance and the resulting material is not a PVA hydrogel. The material is used as wound dressing thus, is not an injectable hydrogel (see Tanihara, col. 3, line 64 through col. 4, line 21; see col. 16, line 48 through col. 21 line 47, for process of making the modified gel and its characteristics usable as wound dressing but not as an injectable hydrogel). Tanihara does not describe a PVA hydrogel because the commonly understood definition of a PVA polymer is one with the majority of monomeric groups consisting of  $-CH_2-CHOH-$ , depending on hydrolyzation of saponification level. The name, PVA is an acronym for poly(vinyl alcohol) and therefore technically requires a molecule that is composed of vinyl alcohol monomers. The "PVA" described by Tanihara contains structural units at mole fractions of 0.05 to 0.5 of the formula I and/or formula II in that patent, and is thus termed a 'copolymer' by those familiar in the art, and cannot be simply described as "PVA" (see Tanihara, col. 3, line 64 through col. 4, line 21). Tanihara claims a wound dressing material of hydrogel containing HA or HA-salt (see claims 1 & 2). The material described by

Tanihara is however not a PVA polymer, and is instead a molecule with a specific pendant group (see formula I).

I further clarify that PVA is defined as the molecule with the vinyl alcohol monomer with some percentage of vinyl acetate and does not refer to PVA copolymers. I refer to the following web-links for additional clarity (hard copies of the web-pages were submitted with the response filed on July 30, 2007):

[http://en.wikipedia.org/wiki/Polyvinyl\\_alcohol](http://en.wikipedia.org/wiki/Polyvinyl_alcohol)

<http://www.socplas.org/industry/defs.htm>

The above entries discuss required modification of PVA in order to make copolymers. Additionally, for example, see Sigma Aldrich source, where there are 39 grades of PVA available, but any molecule that is PVA based with modification is cited as a copolymer.

Moreover, Tanihara requires:

Process 1 (see column 16, line 51), which involves simultaneous or sequential modification of polyvinyl alcohol, thus the product is no longer a polymer; and

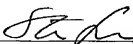
Process 2 (see column 17, line 19) is described as "[t]he homopolymer or copolymer thus is partially saponified... Then, the hydroxyl group of the saponified product produced by saponification is modified to a final 0.0001 to 0.5 molar fraction range..."

Hence, Tanihara disclosure relates to copolymers resulting from the modification by above described processes 1 or 2. Therefore, Tanihara disclosure is not relevant to the claimed invention.

6. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

2/13/2008

Date



Stephen Spiegelberg, Ph. D.